# NON-ALCOHOLIC AND ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS SUFFERING FROM BILIARY TRACT PATHOLOGY AND OBESITY: CLINICAL AND FUNCTIONAL ASPECTS

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***Annotation**. Fatty liver disease of different genesis is very often accompanied by biliary tract pathology and obesity. Clinical and functional characteristics of the fatty liver disease with accompanying biliary tract and obesity pathology include intensity of clinical manifestation and a disease course with a predominance of asthenic, dyspeptic, abdominal pain syndromes, cholestatic syndrome, hepatomegalia, obesity against the background of mild and moderate manifestations of cytolysis and mesenchymal inflammation.*

***Keywords:** fatty liver disease, steatosis, non-alcoholic steatohepatitis, alcoholic steatohepatitis, biliary tract, obesity, clinical findings, diagnostics.*

**Introduction.** Liver involvement due to pathology of hepatobiliary system (HBS) of non-alcoholic and alcoholic etiology is characterized by combination of different etiological and pathogenic mechanisms and belongs to the group of conditions, incorporated under the title "fatty liver disease" (FLD). Formation of FLD of different etiology in patients suffering from biliary tract pathology (BT) and obesity takes place against the background of poor metabolic compensation, activation of lipid peroxygenation processes and reduction in antioxidant protection activity, endogenous intoxication, obesity, insulin resistance or type 2 diabetes mellitus with significant daily fluctuations of glycemia, increase of biliary acids contents in blood serum and characteristic parameters of cytolysis [2, 12, 15].

Currently a non-alcoholic fatty liver disease (NAFLD), prevalence of which is rapidly growing in both economically and socially developed countries, as well as in developing countries [9, 10], is one of the most serious problems of internal medicine in general. Prevalence of NAFLD amounts to 10–40% in the general population, 30–100% — among those suffering from obesity, 20–92 % — among dyslipidemia patients, 10–75 % — among those suffering from type 2 diabetes mellitus [9]. About 30% of patients diagnosed with steatosis develop non-alcoholic steatohepatitis, which in 10% of cases can be subsequently transformed into hepatic cirrhosis [13]. Unfortunately, prevalence of NAFLD in Ukraine is under-investigated. Chronic liver involvements of alcoholic genesis retain their role in the structure of general liver pathology, being currently characterized as alcoholic fatty liver disease (AFLD). Alcohol abuse is an important medical and social problem worldwide, especially in the US, Europe, including in Ukraine. According to statistical data, 4,65 % of Americans meet the criteria for alcohol abuse, while 3,81 % — meet the criteria for alcohol dependence [1, 14]. Daily consumption of alcohol in a dose of more than 60 grams per day leads to development of alcoholic hepatic steatosis (AHS), which in

5–15% of cases progresses to fibrosis and hepatic cirrhosis [6]. 10–35 % of patients, which hospitalized with alcohol abuse, are diagnosed with alcoholic steatohepatitis (ASH) [1, 14]. There are no reliable data on AFLD prevalence in Ukraine.

It was established, that FLD is often associated with inflammatory processes in bile ducts and gallbladder in the form of chronic non-calculous or calculous cholecystitis, as well as with pathological conditions after carrying out of cholecystectomy and obesity [2, 7, 15]. In these instances it is possible to speak of concurrent (comorbid) or conjugated pathology within HBS of non-alcoholic and alcoholic genesis and obesity. Biliary dyskinesia and chronic inflammatory processes of BT are often developed against the background of steatoses and steatohepatitis, thus adding to more severe violations in functions and structure of the liver, which in its turn fosters torpid course of the disease and complications [8].

Clinical manifestations of FLD are minimal. The majority of patients (48–100%) lack symptoms, characteristic of liver disease. There are no specific markers of FLD diagnostics [10, 12]. Quite often FLD is diagnosed after the hepatomegalia or unexplained increase in transaminases has been revealed [12]. Thus, the disease is asymptomatic in most patients, though comorbid course of the disease may be characterized by active clinic manifestation and more complicated course.

Irrespective of the rapid spread of HBS pathology within the population some clinical and functional aspects of FLD of non-alcoholic and alcoholic genesis against the background of biliary tract pathology and obesity, despite the availability of published data, remain not fully investigated. Therefore, the problem of timely diagnostics of FLD in patients, which are suffering from biliary tract pathology and obesity, remains relevant today.

**Objective.** To explore the clinical and laboratory manifestations of FLD of non-alcoholic and alcoholic genesis in patients, which are suffering from biliary tract pathology and obesity.

**Materials and Methods.** 300 patients diagnosed with FLD of non-alcoholic and alcoholic genesis with obesity and accompanying biliary tract pathology: chronic non-calculous cholecystitis (CNCC), chronic calculous cholecystitis (CCC), patients with condition after laparoscopic cholecystectomy and patients with postcholecystectomy syndrome (PCS), in which revealed signs of FLD during sonographic examination or morphological examination of liver biopsy. The age composition of those examined ranged from 24 to 73 years. Predominantly those were the patients of the employable age within the range of 35–59 years. The average age of the patients amounted to 42,1±2,02 years. Sex composition: 147 (49%) men and 153 (51%) women. Duration of the disease ranged from 1 to 30 years. The control group consisted of 20 apparently healthy subjects.

The diagnosis of FLD and CNCC, chronic calculous cholecystitis, postcholecystectomy syndrome was set in compliance with standardized protocols of diagnosis and treatment of digestive diseases according to the Resolution of the Ministry of Health of Ukraine No. 271 as of June 13, 2005 p, ICD-10 and WHO criteria [4], based on the medical background data, clinical and instrumental (ultrasound examination of the abdominal cavity) examination, with due consideration of the data of conventional biochemical parameters [5]. In order to confirm the alcoholic etiology of FLD the CAGE diagnostic test was also applied to [6]. The diagnosis is established by increasing obesity body mass index

over 30 kg/m$^2$ [11]. All the patients have signed the informed consent form to participate in the study.

NAFLD was diagnosed on grounds of increase in liver enzymes level, data of the liver ultrasonography (increase in echogenicity of the parenchyma, increase in echo-signal attenuation, smoothing of vascular pattern, hepatomegalia), exclusion of the viral infection, autoimmune, hereditary liver diseases, influence of hepatotoxic factors [4, 5]. The diagnosis of AFLD was based on combination of characteristic features, and namely on assessment of the patient's complaints, anamnestic data as regards of alcohol abuse (daily consumption of alcohol in a dose of more than 60 grams per day), clinical and laboratory manifestations of liver disease with due consideration of CAGE test parameters [4, 6].

Activity of NASH and ASH was assessed according to serum glutamic pyruvic transaminase (ALAT) level: the minimum level provided increase in serum glutamic pyruvic transaminase (ALAT) amounted to 3-fold normal range, moderate one from 3- to 5-fold normal range, while the high one to more than 5-fold normal range.

In order to objectivize the subjective and objective manifestations of disease among the examined patients we have resorted to assessment of clinical signs using 3-point scale:

0 — absence of clinical syndrome signs;

1 — manifestations of clinical syndrome are minimal and appear not systematically;

2 — manifestations of clinical syndrome are permanent, moderately expressed;

3 — manifestations of clinical syndrome are permanent, expressed, reduce the quality of life and working capacity.

The assessment of liver's functional capacity was carried out using routine methods according to levels of protein metabolism (blood levels of total protein, albumins, globulins and their fractions, thymol test), presence of cholestatic syndrome (level of total bilirubin, alkaline phosphatase (ALP) and cytolytic (activity of aminotransferase — Serum glutamic oxaloacetic transaminase (ASAT) and Serum glutamic pyruvic transaminase (ALAT) syndromes [3].

Analysis of the study results was carried out using Statistica software package and Excel tables with the use of parametric and nonparametric statistical methods. Quantitative indicators provided in the form of the average value and standard error of the mean (M±m). The differences were considered significant provided the level of probability amounted to $p < 0,05$.

**Results and their discussion.** Among 300 of the examined patients, diagnosed with FLD and obesity, 200 (66,7%) were diagnosed with NAFLD, 100 (33,3%) had AFLD. The patients, diagnosed with NAFLD, were split into 100 (33,3%) patients with the set diagnosis of non-alcoholic hepatic steatosis (NAHS-1) and 100 (33,3%) diagnosed with non-alcoholic steatohepatitis (NASH-2). The patients, diagnosed with AFLD, were also split into 50 (16,7%) patients with the registered alcoholic steatosis of liver (AHS-3) and 50 (16,7%) more suffering from alcoholic steatohepatitis (ASH- 4).

Among those patients, which suffering from NASH-1, — 70 (70%) were expressing minimum activity, 30 (30%) patients were diagnosed with moderate activity of the pathological process. In patients, suffering from ASH, the minimum activity was registered in 49 (98%) of the patients, moderate — in 1 (2%) patient. FLD of the patients was diagnosed against the background of biliary tract pathology and obesity.

The patients, suffering from NAFLD, were complaining of general weakness, increased fatigability, psychoemotional instability, manifestations of anhedonia (reduction in activity and vigor, loss of interest and satisfaction from customary things), headaches, frequent mood changes. Symptoms like these in their totality amounted to asthenic syndrome with pronounced autonomic disturbances, diagnosed in 48% of the patients with NAHS-1 and in 63% of patients suffering from NASH-2 (Table 1), being 1,3 times more frequent if to compare to NAHS-1 ($p<0,05$). The degree of severity of the asthenic syndrome was minimum and moderate (Table 2) for the patients with NAHS-1 (0,94±0,11 points on average), as well as moderate and significant in patients suffering from NASH-2 (1,66±0,14 points on average) ($p<0,05$). The development of the asthenic syndrome in patients, suffering from NAFLD and obesity, may be related to metabolic disorders, phenomena of endogenous intoxication with the emergence of average weight molecules and significant disorders of energy metabolism regulation. Prevalence of the main clinical syndromes in patients with NAFLD and AFLD accompanied by biliary tract pathology and obesity is represented at Figure 1. It was established, that from the clinical prospective the majority of patients with NAFLD and obesity complained of constant or periodic nausea or epigastric burning, which arose and got intensified during or after the meals, feeling of bitterness or dryness in the mouth, belching, reduction in complete absence of appetite, distended abdomen, astrictions or diarrhea, as well as unstable stool with alternating constipation with diarrhea. The mentioned symptoms were considered to be manifestations of dyspeptic syndrome, which was registered in 77% of patients diagnosed with NAHS-1 and 80% of patients diagnosed with NASH-2. Dyspeptic syndrome in patients with NAFLD and obesity may be related to violation of detoxification function of the liver, increase in endogenous intoxication and combined damage to biliary and pancreatic systems accompanied by violation in digestive processes.

The data as regards of severity degree of the chief clinical manifestations of disease in patients belonging to thematic groups is provided in Table 2. The degree of severity of the dyspeptic syndrome was minimum and moderate for the patients with NAHS-1 (averagely 1,19±0,08) and moderate and significant in patients diagnosed with NASH-2 (1,82±0,11 on average) ($p<0,05$).

Nausea after meals was registered with equal frequency in patients suffering from NAHS-1 and NASH-2 — 23% and 21% respectively. Similar results pertained to the symptoms of bitterness in the mouth (29% and 26%), epigastric burning (24% and 28%), belching after meals (23% and 24%), which were diagnosed with more or less equal frequency in patients suffering from NAHS-1 and NASH-2 ($p>0,05$). The average degree of severity of nausea after meals was a bit higher in patients diagnosed with NASH-2 and amounted to 0,50±0,10 versus 0,29±0,06 in patients suffering from NAHS-1.

*Table 1*

**Prevalence of major clinical and biochemical syndromes in patients suffering from non-alcoholic and alcoholic fatty liver disease and obesity**

| Syndromes | NAHS-1, n=100 | | NASH-2, n=100 | | $p_{1-2}$ | AHS-3, n=50 | | ASH-4,n=50 | | $p_{3-4}$ | $p_{1-3}$ | $p_{2-4}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Abs. | % | Abs. | % | | Abs. | % | Abs. | % | | | |
| Asthenic | 48 | 48 | 63 | 63 | **<0,05** | 39 | 78 | 32 | 64 | >0,05 | **<0,001** | **<0,05** |
| Dyspeptic | 77 | 77 | 80 | 80 | >0,05 | 47 | 94 | 47 | 94 | >0,05 | **<0,01** | **<0,05** |
| Abdominal pain | 98 | 98 | 94 | 94 | >0,05 | 50 | 100 | 50 | 100 | >0,05 | >0,05 | >0,05 |
| Hepatomegalia | 51 | 51 | 67 | 67 | **<0,05** | 27 | 54 | 34 | 68 | >0,05 | >0,05 | >0,05 |
| Cytolysis | – | – | 100 | 100 | **<0,001** | – | – | 50 | 100 | **<0,001** | >0,05 | >0,05 |
| Cholestatic | 24 | 24 | 45 | 45 | **<0,01** | 26 | 52 | 29 | 58 | >0,05 | **<0,001** | >0,05 |
| Mesenchymal inflammatory | – | – | 55 | 55 | **<0,001** | – | – | 50 | 100 | **<0,001** | >0,05 | **<0,001** |
| Liver cell failure | – | – | 60 | 60 | **<0,001** | – | – | 41 | 82 | **<0,001** | >0,05 | **<0,01** |
| Obesity I-III grade | 69 | 69 | 60 | 60 | >0,05 | 22 | 44 | 33 | 66 | **<0,05** | **<0,01** | >0,05 |

Notes. $p_{1-2}$ – level of differences significance between the indicators of NAHS and NASH groups;
$p_{3-4}$ – between AHS and ASH groups; $p_{1-3}$ – between NAHS and AHS groups; $p_{3-4}$ – between NASH and ASH groups.

*Table 2*

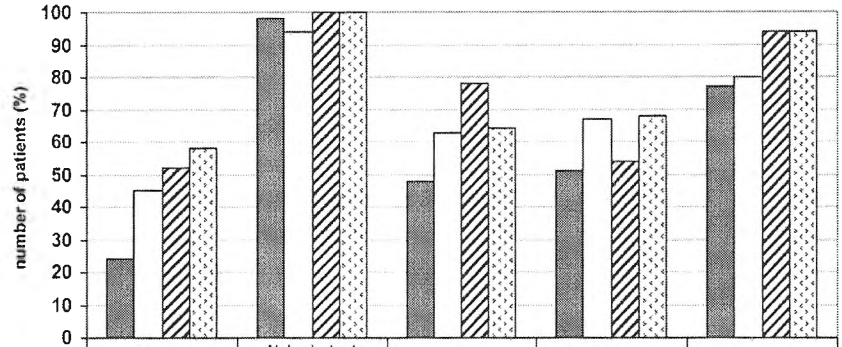
**The degree of severity of the main clinical syndromes in patients suffering from non-alcoholic and alcoholic fatty liver disease and obesity, abs. (%)**

| Syndromes, degree of severity | NAHS-1, n=100 | NASH-2, n=100 | AHS-3, n=50 | ASH-4, n=50 |
|---|---|---|---|---|
| **Asthenic** | | | | |
| -absent (0) | 52 (52%) | 37 (37%) | 11 (22%) | 18 (36%) |
| - minimal (1) | 10 (10%) | 4 (4%) | 16 (32%) | – |
| -moderate (2) | 30 (30%) | 15 (15%) | 21 (42%) | 22 (44%) |
| -considerable (3) | 8 (8%) | 44 (44%) | 2 (4%) | 10 (20%) |
| - average, M±m (Me) | 0,94±0,11 (0) [2] | 1,66±0,14 (2,0) [1,4] | 1,28±0.12 (1,0) [1] | 1,48±0,17 (2,0) |
| **Dyspeptic** | | | | |
| -absent (0) | 23 (23%) | 20 (20%) | 3 (6%) | 3 (6%) |
| - minimal (1) | 38 (38%) | 9 (9%) | 18 (36%) | – |
| -moderate (2) | 36 (36%) | 40 (40%) | 27 (54%) | 34 (68%) |
| -considerable (3) | 3 (3%) | 31 (31%) | 2 (4%) | 13 (26%) |
| - average, M±m (Me) | 1,19±0,08 (1,0) [2,3] | 1,82±0,11 (2,0) [1,4] | 1,56±0,10 (2,0) [1,4] | 2,14±0,10 (2,0) [2,3] |
| **Abdominal pain** | | | | |
| -absent (0) | 2 (2%) | 6 (6%) | – | – |
| - minimal (1) | 22 (22%) | 1 (1%) | 15 (30%) | – |
| -moderate (2) | 60 (60%) | 23 (23%) | 25 (50%) | 29 (58%) |
| -considerable (3) | 16 (16%) | 70 (70%) | 10 (20%) | 21 (42%) |
| - average, M±m (Me) | 1,90±0,07 (2,0) [2,3] | 2,57±0,08 (3,0) [1,4] | 1,90±0,10 (2,0) [4] | 2,42±0,07 (2,0) [2,3] |

Notes. [1,2,3,4] – $p<0,05$ if compared to an appropriate group.

The average degree of bitterness in the mouth before meals was more pronounced in patients suffering from NAHS-1 and amounted to — 0,09±0,03 if to compare to the patients diagnosed with NASH-2 — 0,03±0,03 ($p<0,05$). However, bitterness in the mouth after meals was more frequently diagnosed in patients with NASH-2 — 0,62±0,11 versus 0,43±0,07 in patients suffering from NAHS-1 ($p>0,05$). At the very same time, complaints of distended abdomen of an average degree of severity 1,13±0,13 were more characteristic of patients diagnosed with NASH-2 versus 0,69±0,09 in patients suffering from NAHS-1 ($p<0,05$).

Patients diagnosed with NAFLD were disturbed by feeling of heaviness, feeling of fullness in the right and left subcostal and epigastric areas, pain, which has constant or intermittent nature, tender pain, which intensified after meals or physical loads.




| | Cholestatic | Abdominal pain | Asthenic | Hepatomegalia | Dyspeptic |
|---|---|---|---|---|---|
| NAHS | 24 | 98 | 48 | 51 | 77 |
| NASH | 45 | 94 | 63 | 67 | 80 |
| AHS | 52 | 100 | 78 | 54 | 94 |
| ASH | 58 | 100 | 64 | 68 | 94 |

*Figure 1.* ***Prevalence of the main clinical syndromes in patients suffering from non-alcoholic and alcoholic fatty liver disease accompanied by biliary tract pathology and obesity.***

All the mentioned symptoms formed the abdominal pain syndrome, which in case of NAFLD and obesity may be related to presence of inflammatory infiltration of liver tissue and hepatomegalia. Abdominal pain syndrome was registered in 98% of patients diagnosed with NAHS-1 and 94% of patients diagnosed with NASH-2. The degree of severity of the abdominal pain syndrome was minimum and moderate for the patients with NAHS-1 (1,90±0,07 on average) and moderate and significant in patients suffering from NASH-2 (2,57±0,08 on average), $p<0,05$ (Table 2).

In patients of various groups pain in the right and left hypochondrium and epigastrium was more frequently related to food intake, with pain without any reason ranking second. Pain in the right hypochondrium explained by no reason was more frequently

registered in patients suffering from NAHS-1 — 21% of cases versus 8% of cases in NASH-2 group (p<0,01).

The average degree of severity of the pain syndrome in patients suffering from non-alcoholic and alcoholic fatty liver disease and obesity is given in Table 3. The highest intensity of pain in the right and left hypochondrium after meals was revealed in patients of NASH-2 group — 1,45±0,14 in the right and 0,92±0,13 in the left hypochondrium, what differentiated them from the patients of NAHS-1 group, the average pain degree of which amounted to 1,09±0,11 in the right and 0,51±0,09 in the left hypochondrium (p<0,05).

During the abdominal palpation examination of the patients, who were under observation, the patients of various groups usually revealed moderate tenderness in the right, left subcostal and epigastric areas (Figure 2). To be more specific, tenderness on palpation in the right hypochondrium was diagnosed in almost all the patients having NAFLD — 89% and 81% of cases in NAHS-1 and NASH-2 groups, respectively. However, the average degree of the objective severity of pain in the right hypochondrium (Table 4) was more intense in patients of NASH-2 group (2,16±0,12) if compared to NAHS-1 group (1,71±0,09) provided p<0,05.

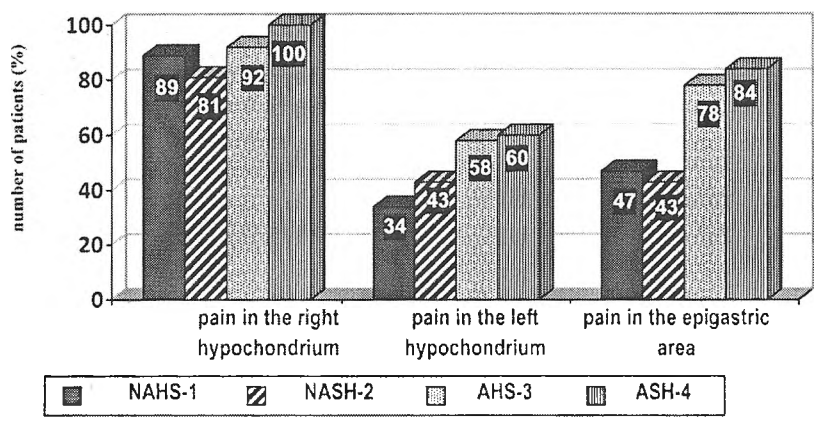



*Figure 2.* ***Frequency distribution of the pain syndrome revealed within physical examination depending on the location.***

Other objective indicators of tenderness in the upper abdominal area — within the area of epigastrium and left hypochondrium — were registered in NAHS-1 and NASH-2 groups with equal frequency, though among fewer patients (from 34% to 47%). As in the previous case, the average degree of pain severity in the left hypochondrium was higher in patients of NASH-2 group (1,10±0,13) if to compare to the patients of NAHS-1 group (0,61±0,09) provided p<0,05.

During the physical examination of patients suffering from NAFLD accompanied by biliary tract pathology and obesity the hepatomegalia was diagnosed. The patients suffering from NASH-2 were more frequently diagnosed with clinical manifestations

of hepatomegalia — 67% of cases, versus 51% of cases among patients belonging to NAHS-1 group ($p<0,05$). On palpation of the liver in patients diagnosed with NAFLD, having no excessive weight, a sharp or slightly rounded edge of the liver was revealed. It was characterized by moderate tenderness and smooth surface, as well as dense or tight elastic consistency. Dimensions of the liver determined by percussion according to Kurloff's approach in patients suffering from NAHS-1 were higher than standard rates (1-st dimension — 12,41±0,2 cm, 2-d dimension — 11,25±0,19 cm, 3-d dimension — 10,13±0,17 cm). In patients diagnosed with NASH-2 the degree of hepatomegalia was more pronounced due to increase in activity of the inflammatory process and was equal to values as follows: 1-st dimension — 13,86±0,24 cm, 2-d dimension — 12,65±0,24 cm, 3-d dimension — 11,41±0,24 cm ($p<0,001$ if compared to NAHS-1 group).

Increase in dimensions of the liver in case of NAFLD and obesity is caused by fat and protein dystrophy, inflammatory swelling of hepatocytes, parenchymal infiltration and development of the liver fibrosis. Objective increase in dimensions of the liver was registered in every second patient in all the observation sub-groups NAHS-1 and NASH-2.

All the data provided above highlight the exacerbation of the pathological process in the liver and biliary tract in patients suffering from NAFLD and obesity in various clinical observation groups.

The comparative analysis of subjective and objective syndromes, inherent to FLD of non-alcoholic and alcoholic etiology, demonstrates (Table 1, Figure 1), that in case of AHS-3 manifestations of asthenic (in 78% of cases) and dyspeptic (in 94% of cases) syndromes are registered more frequent than in patients of NAHS-1 group (respectively in 48%, $p<0,001$ and 77% of cases, $p<0,01$). Similar results were obtained from patients suffering from ASH-4 and NASH-2, in which dyspeptic syndrome was registered in 94% and 80% of cases, respectively ($p<0,05$).

According to the frequency of the asthenic syndrome ASH-4 and NASH-2 groups were statistically comparable (64% and 63% of patients, respectively provided $p>0,05$), however the degree of severity of the mentioned syndrome was significantly higher in patients suffering from NASH — 1,66±0,14 versus 1,48±0,17 ($p<0,05$).

Prevalence of certain clinical syndromes in patients diagnosed with steatosis and steatohepatitis of alcoholic etiology in comparison with groups of patients diagnosed with steatosis and steatohepatitis of non-alcoholic etiology has significantly increased. To be more specific, the highest degree of severity of the dyspeptic syndrome was revealed in patients of ASH-4 group and on average amounted to 2,14±0,10 versus 1,82±0,11 in patients from NASH-2 group ($p<0,05$) and 1,56±0,10 in case of AHS-3 ($p<0,05$).

*Table 3*

**The average degree of severity of the pain syndrome in patients suffering from non-alcoholic and alcoholic fatty liver disease and obesity, M±m (Me)**

| Localization of pain and factors associated with it | NAHS-1, n=100 | NASH-2, n=100 | AHS-3, n=50 | ASH-4, n=50 |
|---|---|---|---|---|
| **Pain in the right hypochondrium** | | | | |
| on an empty stomach | 0,04±0,03 (0) [3] | 0,19±0,07 (0) | 0,22±0,10 (0) [1] | 0,06±0,04 (0) |
| after meals | 1,09±0,11 (1) [2] | 1,45±0,14 (2) [1] | 1,18±0,14 (1) [4] | 1,86±0,15 (2) [3] |
| after physical loads | 0,08±0,04 (0) | 0,06±0,04 (0) | 0,18±0,08 (0) | 0,14±0,08 (0) |
| due to no reasons | 0,40±0,09 (0) | 0,24±0,08 (0) | 0,26±0,11 (0) | 0,18±0,10 (0) |
| **Pain in the left hypochondrium** | | | | |
| on an empty stomach | 0,02±0,02 (0) | 0 | 0,14±0,08 (0) | 0 |
| after meals | 0,51±0,09 (0) [2] | 0,92±0,13 (0) [1] | 0,74±0,14 (0) | 1,04±0,19 (0) |
| after physical loads | 0 [3] | 0,03±0,03 (0) | 0,12±0,07 (0) [1] | 0 |
| due to no reasons | 0,09±0,04 (0) | 0,03±0,03 (0) | 0,20±0,08 (0) | 0,18±0,10 (0) |
| **Pain in the epigastrium** | | | | |
| on an empty stomach | 0,10±0,04 (0) | 0,02±0,02 (0) | 0,16±0,08 (0) | 0,10±0,07 (0) |
| after meals | 0,62±0,10 (0) | 0,75±0,12 (0) | 0,90±0,15 (1) | 1,0±0,17 (0) |
| after physical loads | 0 [3] | 0,03±0,03 (0) | 0,10±0,07 (0) [1] | 0,14±0,08 (0) |
| due to no reasons | 0,07±0,04 (0) | 0,04±0,03 (0) | 0,18±0,08 (0) | 0,18±0,10 (0) |

Notes. [1,2,3,4] – $p<0,05$ if compared to an appropriate group.

*Table 4*

**The average degree of severity of disease objective manifestations in patients suffering from non-alcoholic and alcoholic fatty liver disease and obesity, M±m (Me)**

| Findings of physical examination | NAHS-1, n=100 | NASH-2, n=100 | AHS-3, n=50 | ASH-4, n=50 |
|---|---|---|---|---|
| Tenderness on palpation in the right hypochondrium | 1,71±0,09 (2) [2] | 2,16±0,12 (3) [1] | 1,74±0,12 (2) [4] | 2,40±0,07 (2) [3] |
| Tenderness on palpation in the left hypochondrium | 0,61±0,09 (0) [2,3] | 1,10±0,13 (0) [1] | 1,02±0,14 (1) [1,4] | 1,48±0,18 (2) [3] |
| Tenderness on palpation in the epigastrium | 0,77±0,09 (0) [3] | 1,05±0,13 (0) [4] | 1,36±0,14 (1) [1,4] | 2,02±0,14 (2) [2,3] |
| Tenderness on palpation in the intestine | 0,09±0,05 (0) | 0,23±0,08 (0) | 0,14±0,05 (0) | 0,08±0,04 (3) |
| Hepatomegalia | 0,49±0,05 (0) | 0,51±0,05 (1) [4] | 0,52±0,07 (1) | 0,68±0,07 (1) [2] |

Notes. [1,2,3,4] – $p<0,05$ if compared to an appropriate group.

Intensity of the abdominal pain syndrome was the highest in patients from NASH-2 group — 2,57±0,08 (Table 2), and patients of ASH-4 group — 2,42±0,07 ($p<0,05$ between the groups). The revealed considerable degree of severity of the pain syndrome in patients from NASH-2 group may be explained by presence of moderate activity of the inflammatory process in 30% of the patients diagnosed with NASH-2, while in patients diagnosed with ASH-4 a moderate activity was shown only by 2% of the patients. At the very same time, severity of pain in the right and left hypochondrium after meals was the highest in patients suffering from ASH-4 and amounted to 1,86±0,15 in the right and 1,04±0,19 in the left hypochondrium (Table 4).

The physical examination showed that tenderness on palpation in the right hypochondrium was registered in 100% of patients diagnosed with ASH-4 versus 81% of the patients diagnosed with NASH-2 ($p<0,01$). Tenderness in the left hypochondrium was also more pronounced in patients suffering from AHS-3 and ASH-4 and was registered during the physical examination of 58% and 60% of the patients respectively versus 34% and 43% of those from NAHS-1 ($p<0,01$) and NASH-2 ($p<0,05$) groups. A palpatory pain in the epigastrium was also more frequently registered in patients with AHS-3 (78%) and ASH-4 (84%) rather than in patients diagnosed with NAHS-3 (47%, $p<0,001$) and NASH-4 (43%, $p<0,001$). The physical examination showed approximately equal frequency —54% of patients diagnosed with AHS-3, 68% of patients diagnosed with ASH-4, 51% of patients diagnosed with NAHS-1 and 67% NASH-2 had hepatomegalia. Dimensions of the liver determined by percussion according to Kurloff's approach in patients with AHS-3 were higher than standard rates in apparently healthy subjects and in some cases differed from values of the patients of NAHS-1 group: 1-st dimension — 12,02±0,27 cm in AHS-3 group and 12,41±0,20 cm in NAHS-1 group ($p>0,05$), 2-d dimension — 10,30±0,19 cm and 11,25±0,19 cm

(p<0,01), 3-d dimension — 9,02±0,15 cm and 10,13±0,17 cm (p<0,001). In patients diagnosed with ASH-4 the degree of hepatomegalia was more pronounced if to compare to indicators of apparently healthy subjects. If compared to NASH-2 group the following data was obtained: 1-st dimension — 15,26±0,29 cm in ASH-4 group and 13,86±0,24 cm in NASH-2 group (p<0,001), 2-d dimension — 12,98±0,24 cm and 12,65±0,24 cm (p>0,05), 3-d dimension — 10,97±0,16 cm and 11,41±0,24 cm (p>0,05).

Among biochemical syndromes accompanying FLD of non-alcoholic and alcoholic genesis there were cytolysis, hepatic secretory obstruction, mesenchymal inflammation, distortion of protein synthesis function of the liver (Table 5). Most frequently NASH-2 group patients revealed increased activity of almost all parameters of cytolysis, hepatic secretory obstructiony, mesenchymal inflammation and indicators of distortion of protein synthesis function of the liver if to compare to of the patients of NAHS-1 group (p<0,05). Presence of cytolysis syndrome was typical for 100% of the patients diagnosed with NASH-2 and ASH-4. Most frequently NASH-2 and ASH-4 patients revealed increased activity of serum glutamic pyruvic transaminase (ALAT), which 4,2 and 3,4 times respectively was higher than values demonstrated by apparently healthy subjects (p<0,05) and serum glutamic oxaloacetic transaminase (ASAT) (3,9 times exceedance, p<0,05) in blood serum. More pronounced increase in level of serum glutamic pyruvic transaminase (ALAT) in case of NASH may be explained by presence in this group of the patients revealing minimum and moderate activity of disease; in case of ASH in 98% of cases the patients showing minimum activity of the pathological processes prevailed.

Indicators of total bilirubin in all the patients with FLD and obesity were within the physiological reference range and did not differ from values in apparently healthy subjects. It can only be indicated that total bilirubin was significantly higher in patients suffering from NASH-2 and ASH-4 if compared to patients of NAHS-1 and AHS-3 group (p<0,05).

Changes in the abovementioned values indicate the formation of cytolytic syndrome of minimum or moderate activity in 100% of patients diagnosed with NASH and ASH, which was caused by violation of the structural integrity of hepatocytes among the examined patients. Activity of alkaline phosphatase was increased in patients suffering from NAHS-1 and NASH-2 if compared to apparently healthy subjects group —1,6 (p<0,05) and 2,1 times (p<0,05), respectively. In case of AHS-3 and ASH-4 exceedance of alkaline phosphatase level corresponded to 1,8 and 2,0 times increase (p<0,05).

Contents of biliary acids in blood exceeded standard rates1,6 (p<0,05) and в 1,8 times in case NAHS-1 and NASH-2 (p<0,05). In patients suffering from AHS-3 and ASH-4 the contents of biliary acids also 1,7 (p<0,05) and 2,0 (p<0,05) times respectively exceeded standard rates in apparently healthy subjects.

This being the case, 24% of patients diagnosed with NAHS-1 and 45% of patients diagnosed with NASH-2 revealed cholestatic syndrome (p<0,01). In case of AHS-3 and ASH-4 the phenomena of hepatic secretory obstruction was observed more frequently if to compare to values of the patients from NAHS-1 and NASH-2 groups and

amounted to 52% and 58% respectively ($p_{1-3}$<0,001). The mechanism of cholestatic syndrome development among the examined patients diagnosed with NAFLD and AFLD against the background of biliary tract pathology and obesity consists in reduction in the bile flow into the duodenum due to distortion of bile's synthesis, excretion and clearance and as a result violation of biochemical processes in hepatocytes, manifested as disorder of the processes responsible for capturing and output of bile components.

As may be seen from the Table 5, significant reduction of albumins contents in blood was revealed among patients suffering from NAFLD if compared to standard rates — by 10,2% in case of NAHS-1 (p<0,05) and by 15,8% in case of NASH-2 (p<0,05). If to compare the mentioned groups the differences in values have also been statistically significant (p<0,05). Among patients diagnosed with AHS-3 there were similar results regarding reduction in albumins by 11,0% (p<0,05) if to compare to apparently healthy subjects. The most reduced level of albumins in blood serum was detected in patients diagnosed with ASH-4 — by 19,3% if compared to apparently healthy subjects (p<0,05) and by 9,3% if to compare to AHS-3 group (p<0,05). Reduction in albumin level, being the dominant representative of the protein fraction, witness the distortion of protein synthesis function of the liver among the examined patients accompanied by chronization of the pathological process.

The presence of mesenchymal inflammatory syndrome in case of NASH was indicated by hyper-γ- globulinemia (within the range of 18,1-25,1% (p<0,05), and 17,3- 28,6% in case of ASH (p<0,05), which was diagnosed in majority of cases; increase in thymol test values (2,2 times (p<0,05) — in patients diagnosed with NASH-2, and 2,6 times (p<0,05) provided the diagnosis of ASH-4, as well as reduction in albumin-globulin coefficient (p<0,05).

The presence of mesenchymal inflammatory syndrome in case of NAFLD and AFLD and obesity witness the activation of reticuloendothelial system cells and highlight the activity of the pathological processes.

Obesity of I-III grade, being one of the most spread FLD risk factors (Table 1), was most frequently observed among patients diagnosed with NAHS-1 (69%) and patients with ASH-4 (66%). Values in these groups exceeded the ranges demonstrated by patients with AHS-3 (44%) with $p_{1-3}$<0,01, $p_{3-4}$<0,05. This being the case, 38% were diagnosed with obesity of I grade, 17% — II grade and 14% — III grade among patients suffering from NAFLD. Among patients diagnosed with AFLD the I grade obesity was prevailing; it was diagnosed in 30% of patients, II in 12% and III grade only in 2% of the patients. The obtained data are consistent with the research findings, which convincingly show, that HBS plays an important role in the regulation of body weight, and obesity causes major disturbance in the functioning of the liver and inevitably leads to the development of FLD [2, 13].

*Table 5*

**Indicators of biochemical blood test in patients diagnosed with fatty liver disease** and obesity, **M±m**

| Indicators | Apparently healthy subjects, n=20 | NAHS-1, n=100 | NASH-2, n=100 | AHS-3, n=50 | ASH-4, n=50 |
|---|---|---|---|---|---|
| Total bilirubin, mcmole/l | 12,11±0,74 | 12,74±0,54[2] | 15,66±1,05[1] | 12,20±0,71[4] | 16,93±1,78[3] |
| ALAT, millimole/hour x l | 0,37±0,02 | 0,49±0,05[2] | 1,57±0,13*[1,4] | 0,47±0,02[4] | 1,24±0,07*[2,3] |
| ASAT, millimole/hour x l | 0,17±0,02 | 0,21±0,02[2] | 0,66±0,04*[1] | 0,23±0,02[4] | 0,67±0,04*[3] |
| Alkaline phosphatase, millimole/hour x l | 0,68±0,02 | 1,07±0,06*[2] | 1,43±0,12*[1] | 1,22±0,07* | 1,33±0,09* |
| Biliary acids, millimole/l | 0,18±0,01 | 0,28±0,01*[2] | 0,32±0,01*[1] | 0,33±0,01*[1] | 0,36±0,01*[2,3] |
| Thymol test, conventional units | 2,69±0,22 | 4,05±0,16*[2,3] | 5,90±0,19*[1,4] | 5,78±0,28*[1,4] | 7,07±0,24*[2,3] |
| Total protein, g/l | 79,5±1,0 | 70,2±0,7*[2] | 67,8±0,8*[1,3] | 68,6±0,7*[4] | 65,4±0,8*[2,3] |
| Albumins, % | 58,1±0,7 | 52,2±0,6*[2] | 48,9±0,6*[1] | 51,7±0,7*[4] | 46,9±1,0*[3] |
| Globulins, % | 37,4±0,5 | 45,3±0,4*[2,3] | 48,4±0,6*[1,4] | 49,4±1,0*[1,4] | 54,2±1,4*[2,3] |
| $\alpha_1$, % | 4,39±0,12 | 5,42±0,09*[2,3] | 6,44±0,18*[1] | 6,01±0,24*[1,4] | 7,09±0,39*[3] |
| $\alpha_2$, % | 7,01±0,10 | 8,26±0,12*[2,3] | 9,65±0,19*[1,4] | 9,27±0,20*[1,4] | 10,71±0,32*[2,3] |
| β, % | 10,28±0,14 | 11,54±0,15*[2,3] | 12,69±0,17*[1,4] | 12,57±0,27*[1,4] | 14,01±0,43*[2,3] |
| γ, % | 15,63±0,23 | 20,08±0,15*[2,3] | 20,92±0,22*[1,4] | 21,55±0,49*[1] | 22,38±0,42*[2] |

Notes. * — p<0,05 if compared to control group; [1,2,3,4] — p<0,05 if compared to an appropriate group.

**Conclusions.** This being the case, the clinical features of the chronic comorbid HBS pathology of non-alcoholic and alcoholic genesis were established; it was also found out that FLD is very often accompanied by biliary tract pathology and obesity. Clinical features of NAFLD with accompanying biliary tract pathology and obesity include intensity of clinical manifestation and a disease course with a predominance of asthenic, dyspeptic, abdominal pain syndromes, cholestatic syndrome, hepatomegalia, obesity against the background of minimum and moderate manifestations of cytolysis and mesenchymal inflammation.

**Prospects for further research.** Further research must be directed at improving of NAFLD and AFLD diagnostic criteria in patients suffering from biliary tract pathology and obesity on grounds of parameters of lipid peroxidation, antioxidant defense system, endogenous intoxication and markers of the liver fibrosis.

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